REMARKS

Claims 1, 2, 4-11, 14, 15 and 21-29 are pending. By this Amendment, claim 3 is canceled without prejudice and claims 1 and 29 are amended. Applicants have amended the specification to update references to copending applications that have since issued. Claim 1 has been amended to delete certain types of association to advance prosecution of the application. These features will be prosecuted in a related application. The specification supports the amendment of claim 29, for example, at page 14, lines 23-28. The amendment of claim 29 is not intended to change the claim scope. No new matter is added by the amendments.

All the pending claims stand rejected. Applicants respectfully request reconsideration of the rejection based on the following comments.

Rejections Under 35 U.S.C. §112, First Paragraph

The Examiner rejected claims 1-11 and 29 under 35 U.S.C. §112, first paragraph, as containing subject matter which is not described in the specification in such a way to reasonably convey to one skilled in the relevant art that the inventors, at the time that the application was filed, had possession of the claimed invention. In particular, the Examiner asserts that language added to the claims relating to the crosslinked functional groups lacked original support in the specification. Applicants respectfully request reconsideration of the rejections based on the following comments.

While Applicants believe that the language added to claim 1 in the Amendment of January 29, 2001 is supported by the specification, to advance prosecution of the case, Applicants have amended claim 1 to delete the language objected to by the Examiner.

With respect to claim 29, Applicants have clarified the claim language. Based on this amendment, the support for the language is clear, as noted above with respect to the claim amendment.

In view of the amendments, Applicants respectfully request withdrawal of the rejection of claims 1-11 and 29 under 35 U.S.C. §112, first paragraph, as containing subject matter which is not described in the specification in such a way to reasonably convey to one skilled in the relevant art that the inventors, at the time that the application was filed, had possession of the claimed invention.

Rejections Under 35 U.S.C. §112, Second Paragraph

The Examiner rejected claims 1-11 and 29 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. Specifically, the Examiner indicated that the subject matter added to the claims did not have explicit support. Furthermore, the Examiner indicated that the terminology "intrinsically active" in claim 29 was unclear. Applicants respectfully request reconsideration of the rejections based on the following comments.

With respect to the terminology "intrinsically active," this language has been replaced. Applicants believe that amended claim 29 is clear.

With respect to the Examiner's indication that the claim language does not have "explicit support," Applicants are not aware of any statutory or judicial doctrine that requires "explicit support." To the extent that this remains an issue following the above amendments, Applicants respectfully request citation of explicit statutory language or case law to clarify the requirement of "explicit support." However, Applicants believe that the present claims are clear, as required under 35 U.S.C. §112, second paragraph.

Applicants respectfully request withdrawal of the rejection of claims 1-11 and 29 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention.

Obviousness-Type Double Patenting

The Examiner provisionally rejected claims 1-6, 9-11, 14 and 21-29 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 3, 4, 8-11, 13 and 15 of copending Application 09/186,810.

Applicants will consider filing a Terminal Disclaimer when the claims have been found otherwise allowable.

Rejections Under 35 U.S.C. §102(b) Over Cahalan

The Examiner rejected claims 25 and 28 under 35 U.S.C. §102(b) as being anticipated by U.S. Patent 5,308,641 to Cahalan (the Cahalan patent). The Examiner indicated that the solid surface included human or animal tissue and the biomolecule could be a growth factor listed in the Cahalan patent. Applicants respectfully request reconsideration of the rejection based on the following comments.

The Cahalan patent discloses a variety of substrates. The primary focus of the discussion in the Cahalan patent is on the use of polymer substrates. See, for example, the Examples in the Cahalan patent. In a general list of possible substrates, the Cahalan patent includes "human or animal tissue such as bone, skin and teeth". See column 4, lines 32-33. The Cahalan patent does not disclose or otherwise suggest or motivate crosslinked tissues as claimed in claim 25. Therefore, the Cahalan patent does not anticipate claims 25 and 28.

The Examiner noted that fixed and crosslinked are used similar in the related art. The Cahalan patent stress that the glutaraldehyde used to perform their process involves "a light crosslinking" over just a few minutes. See for example, column 4, lines 66-69 and column 5, lines 9-10. In contrast, crosslinked tissue, as used in the art, implies that the tissue involves a crosslinked network throughout the tissue material. Crosslinking of tissue involves contacting the tissue with glutaraldehyde for many hours of time. This is described in the text Collagen, Volume III, Biotechnology, pages 2, 3 and 13, a copy of which is enclosed with this amendment. Therefore, the Cahalan patent does not disclose crosslinked tissue.

Applicants respectfully request withdrawal of the rejection of claims 25 and 28 under 35 U.S.C. §102(b) as being anticipated by the Cahalan patent.

Rejections Under 35 U.S.C. §102(b) Over Bayne et al.

The examiner rejected claims 25 and 26 under 35 U.S.C. §102(b) as being anticipated by EP application 0476983 to Bayne et al. (the Bayne EP application). The Examiner asserts that the Bayne EP application discloses application of a fibrin coating prior to a VEGF II growth factor on the surface of a fixed umbilical cord vein. Applicants believe that there has been a misunderstanding regarding the nature of the disclosure in the Bayne patent. Applicants respectfully request reconsideration of the rejection over the Bayne patent in view of the following comments.

The Bayne EP application describes the application of **cells** cultured in VEGF II, not VEGF II itself, with fixed umbilical vein at page 8, line 19. The Bayne EP application discloses application of growth factors to an "artificial surface." However, Applicants were unable to identify the application of VEGF II to fixed tissue in the Bayne EP application. Since the Bayne EP application does not disclose crosslinked tissue with associated polypeptide growth factor, the Bayne EP application does not anticipate claims 25 and 26. Applicants respectfully request withdrawal of the rejection of claims 25 and 26 under 35 U.S.C. §102(b) as being anticipated by the Bayne EP application.

Rejections Over Bayne et al and Wadstrom

The Examiner rejected claims 1-5, 9-11 and 29 under 35 U.S.C. §103(a) as being unpatentable over the Bayne EP application in view of U.S. Patent 5,631,011 to Wadström (the Wadström patent). The Examiner cited the Bayne EP patent for disclosing a fibrin coating applied to a surface prior to the application of VEGF II growth factor. The Examiner cited the Wadström patent for disclosing the use of fibrin as a common biologic tissue adhesive. Applicants believe that there has been a misunderstanding regarding biologic adhesives.

Applicants respectfully request reconsideration of the rejection based on the following comments.

Fibrin is well established as an adhesive product from the adhesive components fibrinogen and thrombin. As described in the Wadström patent at column 1, lines 18-28, thrombin cleaves fibrinogen to form a "fibrin coagulum". This fibrin coagulum is an adhesive, which remains an adhesive while the spontaneous polymerization process takes place. **Once the polymerization is complete and fibrin is formed, the fibrin is not an adhesive.** A careful reading of the Wadström patent leads to this conclusion and is consistent with known properties of the material. Thus, neither the Wadström patent nor the Bayne EP patent teach or suggest using a biologic adhesive for associating a growth factor with a tissue.

Since the cited references do not teach or suggest forming a prosthesis using a biologic adhesive to associate a growth factor with the prosthesis, the cited references do not render the claimed invention obvious. Applicants respectfully request withdrawal of the rejection of claims 1-5, 9-11 and 29 under 35 U.S.C. §103(a) as being unpatentable over the Bayne EP application in view of the Wadström patent.

Rejections Over Bayne et al., Wadström, and Carpentier

The Examiner rejected claims 6-8, 14, 15, 21-24 and 27-28 under 35 U.S.C. §103(a) as being unpatentable over the Bayne EP application and the Wadström patent as applied to claims 1-5, 9-11 and 29 and further in view of U.S. Patent 5,263,992 to "Carpentier" (the Carpentier/Guire patent). The Examiner cited the Carpentier patent for disclosing uncrosslinked and crosslinked forms of tissue, heart valve tissue forms and other types of tissue known in the art. The Examiner asserted that it would be obvious to use these materials as the substrate in the Bayne EP application. However, U.S. Patent 5,263,992 is a patent to Guire. A patent to Carpentier et al. of record has a patent number of 4,648,881. Since it is unclear which of these

two patents was intended, Applicants consider both of these patents. Applicants respectfully request reconsideration of the rejection based on the following comments.

As noted above with respect to claim 1, the Bayne EP application and the Wadström patent do not teach or suggest associating growth factors with substrates using the approaches specified in Applicants' claims. The Guire patent and the Carpentier patent similarly do not teach or suggest the binding of growth factors to a material using the claimed approaches. Therefore, the combined disclosures of the cited patents do not render Applicants' claimed invention of claims 6-8, 14, 15 and 21-24 obvious.

With respect to claims 27 and 28, Applicants noted above that the Bayne EP application does not disclose the association of growth factors with fixed tissue. The other cited references similarly do not teach or suggest the association of growth factors with crosslinked tissue. Therefore, the combined disclosures of the Bayne EP application, the Wadström patent, the Guire patent and the Carpentier patent do not render claims 27 and 28 obvious.

In view of these comments, Applicants respectfully request withdrawal of the rejection of claims 6-8, 14, 15, 21-24 and 27-28 under 35 U.S.C. §103(a) as being unpatentable over the Bayne EP application and the Wadström patent, and further in view of the Carpentier patent and the Guire patent.

Rejections Under 35 U.S.C. §103(a) Over Cahalan

The Examiner rejected claims 1-5 and 11 under 35 U.S.C. §103(a) as being unpatentable over the Cahalan patent alone. The Examiner noted that the Cahalan patent does not disclose allograft or xenograft tissue. However, the Examiner took the position that the use of allograft or xenograft tissue would be obvious absent a showing of criticality. Applicants have amended claim 1 to advance prosecution of the case. Applicants respectfully request reconsideration of the rejections based on the following comments.

The Cahalan patent does not teach or suggest biologic adhesives, antibody-antigen associations, specific binding protein-receptor associations or enzyme-substrate associations. Applicants' claims have been amended to specify these particular types of associations. Since the Cahalan patent does not teach or suggest claimed features of the invention, the Cahalan patent does not render the present claims obvious. Applicants respectfully request withdrawal of the rejection of claims 1-5 and 11 under 35 U.S.C. §103(a) as being unpatentable over the Cahalan patent alone.

CONCLUSIONS

In view of the foregoing, it is submitted that this application is in condition for allowance. Favorable consideration and prompt allowance of the application are respectfully requested.

The Examiner is invited to telephone the undersigned if the Examiner believes it would be useful to advance prosecution.

Respectfully submitted,

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Peter S. Dardi

ATTACHMENT
REDLINED AMENDMENT

Specification As Amended

Please substitute the following amended paragraph(s) and/or section(s):

At page 17, line 13-line 29, the paragraph was amended as noted below:

Alternatively, the polyvalent ions can be associated with exogenous storage structures which are in turn associated with the substrate. The use of exogenous storage structures for the storage of anticalcification metal ions is described in copending, commonly assigned patent applications Serial Nos. 08/595,402, now U.S. Patent 6,193,749, and 08/690,661, both incorporated herein by reference. Similarly, certain metals such as silver have been associated with antimicrobial activity. Exogenous storage structures can be used to store suitable antimicrobial metal ions in association with a substrate as described in copending and commonly assigned patent application Serial No. 08/787,139, now U.S. Patent 6,013,106, incorporated herein by reference. Preferred exogenous storage structures include, for example, ferritin and other metal storage proteins. The exogenous storage proteins can be associated with the substrate in ways similar to those used for VEGF. The activities should not interfere with each other.

Claims As Amended

Please cancel claim 3 without prejudice or disclaimer.

Please substitute the following amended claims for those currently pending:

1. (Five Times Amended) A prosthesis for a human patient comprising allograft or xenograft tissue having a polypeptide growth factor associated therewith by a biologic adhesive, [covalent bonding using a crosslinking agent comprising a plurality of functional groups with same

functionalities,] antibody-antigen associations, specific binding protein-receptor associations or enzyme substrate associations, said polypeptide growth factor being effective to stimulate the affiliation of viable cells with said tissue.

29. (Once Amended) A prosthesis for a human patient comprising allograft or xenograft tissue having a polypeptide growth factor associated therewith by a biologic adhesive, covalent bonding using crosslinking agents comprising a plurality of reactive functional groups [that are intrinsically active], antibody-antigen associations, specific binding protein-receptor associations or enzyme substrate associations, said polypeptide growth factors being effective to stimulate the affiliation of viable cells with said tissue.